Re-evaluation Decision RVD2011-01

Tralkoxydim

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Re-evaluation Decision for Tralkoxydim

After a re-evaluation of the herbicide tralkoxydim, Health Canada's Pest Management Regulatory Agency (PMRA) under the authority of the *Pest Control Products Act* and Regulations is proposing continued registration for the sale and use of products containing tralkoxydim in Canada.

An evaluation of available scientific information found that products containing tralkoxydim have value in the food and crop industry and do not present unacceptable risks to human health or the environment. As a condition of the continued registration of tralkoxydim use on terrestrial food and feed crops, new risk reduction measures are proposed for inclusion on the labels of all tralkoxydim products, and additional data are not being requested at this time.

The PMRA's pesticide re-evaluation program considers potential risks, as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the detail of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

The regulatory approach regarding the re-evaluation of tralkoxydim was first proposed in the consultation document[1] Proposed Re-evaluation Decision PRVD2009-08, *Tralkoxydim* (26 June 2009). This Re-evaluation Decision[2] describes this stage of the PMRA's regulatory process concerning the re-evaluation of tralkoxydim and summarizes the Agency's decision, the reasons for it and, in Appendix II, a summary of comments received during the consultation process and the PMRA's response to these comments. This decision is consistent with the proposed re-evaluation decision stated in Proposed Re-evaluation Decision, PRVD2009-08, *Tralkoxydim* (26 June 2009). To comply with this decision, registrants of tralkoxydim products will be informed of the specific requirements affecting their product registration(s) and of the regulatory options available to them.

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions or proposed conditions of registration.[3] The Act also requires that products have

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Tralkoxydim?

Tralkoxydim is a selective systemic herbicide. It is registered for postemergent use on terrestrial food and feed crops. Tralkoxydim can be used to control a broad spectrum of weeds. It is applied once per year at a rate of 200 g a.i./ha by ground and aerial equipment.

Health Considerations

Can Approved Uses of Tralkoxydim Affect Human Health?

Additional risk-reduction measures are required on tralkoxydim labels. Tralkoxydim is unlikely to affect human health when used according to the revised label directions.

Potential exposure to tralkoxydim may occur through the diet (food and water) or when handling and applying the product. When assessing health risks, two key factors are considered: the levels where no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing, are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed, when tralkoxydim products are used according to label directions.

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[4] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

Tralkoxydim was of slight to moderate acute toxicity by the oral route of exposure in rats and mice. Tralkoxydim was a mild skin and eye irritant in rabbits while it was not a potential skin sensitizer in guinea pigs. Consequently, the following warning statements should appear on the label of the technical product: "Caution Poison, Skin and Eye Irritant".

In rats, there was evidence of oncogenicity in the form of benign Leydig-cell tumours in males and uterine adenocarcinomas in females. In female hamsters, benign liver and and ovarian tumours were noted. There was no treatment-related increase in the number of tumours in male hamsters. Tralkoxydim was not genotoxic and induced no signs of neurotoxicity. Tralkoxydim was teratogenic at a level that resulted in severe maternal toxicity in both rats and rabbits. The main target of toxicity for all species evaluated was the liver. At higher dose levels, the endocrine organs also appear to be targeted by tralkoxydim. When tralkoxydim was given to pregnant animals, effects on the developing fetus were observed at doses that were toxic to the mother, indicating that the fetus is not more sensitive to tralkoxydim than the adult animal.

The risk assessment protects against these effects by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Human exposure to tralkoxydim was estimated from residues in food and drinking water, including the most highly exposed subpopulation (for example, infants smaller than one year old and children 1–2 years old). This aggregate exposure (i.e. to tralkoxydim from food and drinking water) represents less than 2% of the acute reference dose and less than 1% of the chronic reference dose.

The lifetime cancer risk was 3.0×10^{-7} and is considered acceptable. A lifetime cancer risk that is below 1×10^{-6} is considered acceptable for the general population when exposure occurs through pesticide residues in or on food, and to otherwise unintentionally expose individuals. Further information on how the potential cancer risks from pesticides are assessed can be found in Science Policy Notice SPN2000-01, *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*.

The *Pest Control Products Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established through the evaluation of scientific data under the *Pest Control Products Act.* Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

MRLs for tralkoxydim are currently specified for wheat and barley or processed foods derived from these foods. Where no specific MRL has been established, a default MRL of 0.1 ppm applies, which means that pesticide residues in a food commodity must not exceed 0.1 ppm. The current MRLs for tralkoxydim can be found in the Science Evaluation of Proposed Re-evaluation Decision PRVD2009-08, *Tralkoxydim* (26 June 2009).

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern.

Tralkoxydim is not registered for use in any residential areas. Therefore, there are no potential residential or other non-occupational risks.

Occupational Risks from Handling Tralkoxydim

Occupational risks are not of concern.

Cancer and non-cancer risk estimates associated with mixing, loading and applying activities for proposed label uses are not of concern and additional personal protective equipment are not required beyond what is currently specified on the label.

Postapplication risks are not of concern to workers.

Cancer and non-cancer risks to workers re-entering areas treated with tralkoxydim are not of concern. The minimum 12-hour restricted-entry interval (REI) is proposed for all uses.

Environmental Considerations

What Happens When Tralkoxydim is introduced Into the Environment?

Tralkoxydim poses a potential risk to terrestrial plants, therefore additional risk-reduction measures need to be observed.

When tralkoxydim is released into the environment some of it finds its way into soil and water. However, the chemical is not expected to persist as it is rapidly broken down by soil microbes and by chemical reaction in water. Based on adsorption data, tralkoxydim and some of its transformation products are mobile and hence can move freely in soil. Soil column leaching experiments however, indicate that the mobility of tralkoxydim through soil is limited. Under

field conditions, tralkoxydim is shown to dissipate quickly with no residues detected below 10 cm of soil depth beyond 30 days. Although there is no monitoring data available for tralkoxydim to confirm or refute its presence in groundwater, modeling data indicate that tralkoxydim does not leach to groundwater. Based on laboratory, field and modeling data, tralkoxydim is not expected to pose a risk to groundwater contamination. Water runoff on the soil surface can also move the residues into nearby bodies of water, for example, ponds and rivers. Tralkoxydim has not been detected in surface water; however, Canadian water monitoring data of tralkoxydim is limited. Several tralkoxydim transformation products are expected to be formed in soil and aquatic systems. The major transformation products of tralkoxydim are not expected to be a concern to terrestrial and aquatic life.

Tralkoxydim is not expected to pose a risk to wild birds and mammals, bees, other arthropods, fish, amphibians, invertebrates, aquatic plants and algae. However, tralkoxydim does present a risk to sensitive terrestrial plant species that may be exposed to the chemical as a result of spray drifting. To reduce the effects of tralkoxydim in the environment, buffer zones and precautionary label statements are required.

Value Considerations

What is the Value of Tralkoxydim?

Tralkoxydim controls a broad spectrum of grassy weeds in major cereal crops.

In Canada, tralkoxydim has been one of the widely used herbicides (Group 1 graminicide) in cereal crop production since it was first registered in 1992. It is the only graminicide registered for use in perennial cereal rye in the year of crop establishment and in cereals underseeded to forage legumes such as alfafa, birdsfoot trefoil, sainfoin and clovers. Tralkoxydim can be tank-mixed with several broadleaf herbicides to broaden the spectrum of weed control. In addition, it can also be tank-mixed with insecticides for one pass weed and insect control. Tralkoxydim reduces a portion of the economic losses incurred by weeds estimated at $368 million in the early 1990s for barley, wheat and rye in Canada. Although tralkoxydim plays a role in mitigating resistance development in weeds to other herbicide groups, consideration has to be given to resistance management as three species of grassy weeds have already been reported to be resistant to the widespread and frequent use of this graminicide in Canada.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Risk-reduction measures are being implemented to address potential risks identified in this assessment. These measures, in addition to those already identified on existing tralkoxydim product labels, are designed to further protect human health and the environment. Registrants will be asked to amend their labels to reflect these additional measures. The additional key risk-reduction measures that will be required are as follows:

Additional Key Risk-Reduction Measures:

Human Health

- Additional label statements to clarify the maximum number of applications per year.
- A restricted-entry interval to protect workers entering treated sites.
- Statements for personal protective equipment are updated and standardized between the product labels.

Environment

- Additional advisory statements to protect non-target terrestrial plants and to reduce the potential for tralkoxydim in runoff to adjacent aquatic habitats.
- Buffer zones for terrestrial habitats.

What Additional Scientific Information is Being Requested?

No additional data are being requested at this time.

Other Information

The relevant test data on which the decision is based are available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa). For more information, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this decision on tralkoxydim within 60 days from the date of publication of this Re-evaluation Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision, http://www.hc-sc.gc.ca/cps-spc/pest/part/protect-proteger/publi-regist/index-eng.php#rrd), or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act*.

Appendix I Label Amendments for Commercial Class Products Containing Tralkoxydim

A) Label Changes Relating to Human Health

GENERAL LIMITATIONS

PRECAUTIONARY STATEMENTS

PROTECTIVE CLOTHING AND EQUIPMENT:

- Workers must wear coveralls over long-sleeved shirt, long pants and chemical resistant gloves when mixing, loading and during clean up or when adjusting or repairing the sprayer.
- Applicators must wear long-sleeved shirt and long pants.

RESTRICTED-ENTRY INTERVAL:

- For all uses, **DO NOT** enter or allow worker entry into treated areas during the restricted-entry interval (REI) of 12 hours.

DIRECTIONS OF USE

- Only one application per season is permitted.

- Apply only when the potential for drift to areas of human habitation or areas of human activity such as houses, cottages, schools and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

B) Label Changes Relating to Environment

Add to **ENVIRONMENTAL HAZARDS**:

> **TOXIC** to non target terrestrial plants. Observe buffer zones specified under **DIRECTIONS FOR USE**.

The following is required as a standard label statement for runoff:

> To reduce runoff from treated areas into aquatic habitats avoid application to areas with a moderate to steep slope, compacted soil or clay.
>
> Avoid application when heavy rain is forecast.
>
> Contamination of aquatic areas as a result of runoff may be reduced by including a vegetative strip between the treated area and the edge of the water body.

Add to **DIRECTIONS FOR USE**:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.

Aerial application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply when wind speed is greater than 16 km/h at flying height at the site of application. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. To reduce drift caused by turbulent wingtip vortices, the nozzle distribution along the spray boom length **MUST NOT** exceed 65% of the wing or rotorspan.

Buffer Zones:

The buffer zones specified in the table below are required between the point of direct application and the closest downwind edge of sensitive terrestrial habitats (such as grasslands, forested areas, shelter belts, woodlots, hedgerows, riparian areas and shrublands).

Method of Application	Buffer Zones (metres) Required for the Protection of:
	Terrestrial Habitat
Field Sprayer*	3
Aerial (fixed-wing)	100
Aerial (rotary-wing)	80

* For field sprayer application, buffer zones can be reduced with the use of drift reducing spray shields. When using a spray boom fitted with a full shield (shroud, curtain) that extends to the crop canopy, the labelled buffer zone can be reduced by 70%. When using a spray boom where individual nozzles are fitted with cone-shaped shields that are no more than 30 cm above the crop canopy, the labelled buffer zone can be reduced by 30%.

When a tank mixture is used, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture.

Appendix II Comments and Responses

The PMRA received comments in response to PRVD2009-08 from stakeholders which may include registrants, non-governmental organizations with interests in human health or the environment, provincial governments, users of tralkoxydim, and the general public. Some contained additional data or information for consideration by the PMRA. The PMRA has consolidated and summarized the comments received and provides responses below.

1. Comment Relating to the Dermal Toxicity Study, PRVD Sections: 3.1 and 3.2.1

A 21-day dermal toxicity study was submitted to the PMRA for consideration as it was believed that this study was not reviewed by the PMRA prior to publication of the proposed re-evaluation decision.

PMRA Response

The 21-day dermal toxicity study conducted with Wistar rats (PMRA 1581254) was reviewed by the PMRA after the publication of the PRVD. In this repeat-dose dermal toxicity study, tralkoxydim was applied to the shaved skin of Wistar rats at dose levels of 0, 10, 100 or 1000 mg/kg bw/day. Exposure to tralkoxydim by the dermal route had no effect on mortality, clinical signs of toxicity, food consumption, body weight, body weight gain, organ weights, gross and microscopic pathology. Signs of skin irritation were noted in animals from both the control and tralkoxydim-exposed groups and were not considered treatment-related. Decreases in total white blood cell/leucocyte and lymphocyte counts were noted in both males and females exposed to tralkoxydim as compared to control animals. Females in the mid- and high-dose groups also experienced a decreased number of neutrophils. Although the thymus was not weighed, there were no microscopic changes to the thymus that would have suggested that the immune system was a possible target of tralkoxydim. Thus, in and of themselves these alterations were considered insufficient to support a LOAEL. This study was considered acceptable for risk assessment purposes and a NOAEL of 1000 mg/kg bw/day was established and has been considered in the updated re-evaluation. With the review of this study complete, the requirement for a short-term dermal study has been satisfied. The reference list has also been updated to reflect the inclusion of this study in the re-evaluation.

With the acceptance of this 21-day dermal toxicity study, the short- and intermediate-term dermal risk assessment of tralkoxydim presented in PRVD2009-08 was revisited. Previously, a developmental toxicity study conducted with Wistar rats (PMRA 1223665, 1230099 and 1230100) was used for the dermal risk assessment. The developmental NOAEL of 3 mg/kg bw/day was selected with reduced ossification in the absence of maternal toxicity noted at the LOAEL of 30 mg/kg bw/day. A target MOE of 100, accounting for standard uncertainty factors (10-fold for intraspecies variability and 10-fold for interspecies extrapolation), was applied. In PRVD2009-08, a dermal absorption value of 30% was selected based on the studies submitted to the PMRA.

It is acknowledged that the dermal study is relevant to the dermal risk assessment by nature of the route of exposure. However, it should be noted that the endpoint of concern identified through oral testing, namely developmental toxicity, was not assessed by the dermal route of exposure. The data suggests that dermal absorption would have to be significantly lower (i.e. less

than 2%) than that previously established in order for the dermal study to be protective of potential developmental toxicity in risk assessment. As the PMRA has determined that no significant change in dermal absorption is warranted, the previous short- and intermediate-term dermal risk assessment remains unchanged in order to be protective of worker populations that included pregnant and/or lactating women. Therefore, using the rat developmental toxicity study with a NOAEL of 3 mg/kg bw/day and a target MOE of 100, the PMRA considers the dermal risk assessment to be protective of worker populations that include pregnant and/or lactating women.

2. Comment Relating to the Dermal Absorption (PRVD Section 3.2.2)

A dermal absorption factor of 30% was selected by PMRA based on a rat in vivo study (Prout, 1990). The comment received indicated that this was an overestimate of the amount of tralkoxydim that can be absorbed following dermal exposure based on the results of a rat and human in vitro study. A dermal absorption value of 0.49% and 0.88% for the concentrate and field-use dilution was recommended.

PMRA Response

The PMRA reviewed the in vitro dermal absorption studies (human, rat) submitted during the consultation period (Davies, 2000a,b), as well as a human in vitro dermal absorption study available in the current database (Johnson, 2005).

Currently, in vitro animal and/or human data alone are considered insufficient by the PMRA for determining the dermal absorption pattern of a given pesticide; however, they may be useful when combined with other information in a weight-of-evidence approach, such as with in vivo data in a triple pack approach.

When in vitro data are being submitted, it is recommended that they be submitted as part of a triple pack of in vitro human and animal studies and an in vivo animal study (NAFTA, 2008). Under this triple pack approach, if an in vitro technique performed using animal skin is shown to be a good predictor of animal in vivo dermal absorption for a particular compound, then the same technique conducted in vitro with human skin may be useful in extrapolating to humans. In other words, when laboratory studies demonstrate that the ratio of the animal in vitro to in vivo dermal absorption factor is close to 1, a human in vitro study conducted under the same conditions as the animal test is likely to be a good predictor of human dermal absorption. The usefulness of the data would necessarily be dependent on the validity and applicability of the experimental design and the quality and integrity of the data. Consideration of the 'minimal standards' discussed in the position paper (such as same dose/duration regime), would also be given prior to acceptance of the triple pack approach.

The submitted in vitro studies were considered along with the in vivo study (Prout, 1990) as part of a 'triple pack approach'. As summarized in Table 1, the rat in vitro study does not appear to be a good predictor of absorption seen in the rat in vivo study. This could be due to the different doses and formulations in the studies. Formulants have been shown to effect dermal penetration (Bronaugh and Franz, 1986).

As the submitted in vitro dermal absorption studies did not meet the criteria for the 'triple pack approach' the dermal absorption value of 30% from the rat in vivo study cannot be further refined at this time.

Table 1 Summary Comparison of In vitro and In vivo Dermal Absorption Studies for Tralkoxydim

Study	Dose ($\mu g/cm^2$)	Vehicle	Exposure Time (h)	% Absorbed[a]
Rat In vivo				
Prout, 1990	10	Formulation blank (CTL: Y02140/061/001)	10, 24	15.7% @ 10h 18.0% @ 24h
	1			15.8% @ 10h 15.3% @ 24h
	0.1			29.7% @ 10h 35.7% @ 24h
Rat In vitro				
Davies, 2000a	5330	Formulation blank (CTL: Y02140/096)	24	0.85 %
	57.3			49.9%
Human In vitro				
Davies, 2000b	5330	Formulation blank (CTL: Y02140/096)	24	0.26%
	57.3			3.28%
Johnson, 2005	4000	Formulation blank (CTL: Y02140/100)	8, 24	0.072% @ 8h 0.12% @ 24h
	20.1			0.97-1.93% @8h[b] 1.62-2.09% @ 24h[b]

CTL= the CTL reference number for the blank formulation

[a] For the in vivo study, this is sum of blood, carcass, urine, faeces, cage wash, and skin test site. For in vitro studies, this is the sum of amount in receptor fluid, tape strips (for human studies) and amount in skin/epidermis

[b] A range of values is reported as this dose with performed both with and without adjuvant.

3. Comment Relating to the Achieved Dose of the Multigenerational Study, PRVD Section: Appendix IIIA

There was disagreement with the values for the mg/kg bw/day dose achieved in the 3-generation reproduction study in rats.

PMRA Response

The 3-generation reproduction study conducted in Wistar rats (PMRA 1223655 and 1223674) was previously reviewed by the PMRA and was found to be acceptable for risk assessment purposes. This multigeneration reproduction study exposed Wistar rats to tralkoxydim at dietary concentrations of 0, 50, 200 or 1000 ppm. At the time of the study review, the PMRA used standard conversion factors to estimate the administered dose in terms of mg/kg bw/day. The data Syngenta Crop Protection Canada, Inc. recently submitted has been reviewed. The PMRA finds the newer values for the achieved doses to be acceptable and as a result, the NOAELs for parental, reproductive and offspring toxicity were changed to 19.7 mg/kg bw/day instead of the previously used estimated dose of 10 mg/kg bw/day. Changes to the re-evaluation documentation have been made to reflect this.

4. Comment Relating to the Endpoints in 90-day Hamster Study, PRVD Section: Appendix IIIA

There was disagreement with the proposed NOAEL/LOAEL established by the PMRA in the 90-day dietary toxicity study conducted in hamsters. A NOAEL of 350 mg/kg bw/day was proposed, calling the effects noted at that dose level as variable or adaptive.

PMRA Response

The PMRA previously reviewed a 90-day dietary toxicity study conducted with Syrian hamsters (PMRA 1230089 and 1230090). In this study, hamsters were exposed to tralkoxydim at estimated dosages of 0, 18, 55, 140, 350, 700 or 1400 mg/kg bw/day. The effects noted at dose levels up to and including 140 mg/kg bw/day were not considered adverse by the PMRA. In both male and female hamsters exposed to tralkoxydim at 350 mg/kg bw/day, increased relative liver weights and decreased number of lymphocytes were noted. Male hamsters also experienced an increase in the smooth endoplasmic reticulum volume in centrilobular hepatocytes and loss of hepatocyte vacuolation at that same dose level. Taken together, the effects on the liver in males at 350 mg/kg bw/day are consistent with those noted at the higher dose levels and may indicate that a threshold for toxicity was reached at this dose level. Due to the fact that the liver was the main target organ for tralkoxydim, these effects noted in males were considered treatment-related and adverse. As a result, the LOAEL of 350 mg/kg bw/day will be retained for males for risk assessment purposes. Since complete histopathology was not performed at 140 mg/kg bw/day, a NOAEL could not be determined in this study. In contrast to the males, the effects noted in females at 350 mg/kg bw/day were considered adaptive and non-adverse and as such a NOAEL of 350 mg/kg bw/day was established for female hamsters in this study.

5. Comment Relating to the Two Year Rat Study, PRVD Sections: Health Considerations; 3.1; 3.2.2; Appendix IIIA

Comment received recommended utilizing a margin of exposure approach instead of a linear risk assessment (Q*) approach for the two year chronic toxicity/carcinogenicity study conducted with rats for the cancer risk assessment of tralkoxydim.

PMRA Response

In the proposed PRVD2009-08, a cancer risk assessment was conducted by the PMRA. It was stated that in the absence of mode of action data to support a threshold approach, a linear low dose extrapolation approach (Q*) would be used for the re-evaluation of tralkoxydim.

The PMRA found the 2 year chronic toxicity/carcinogenicity study in Wistar rats to be acceptable for risk assessment purposes (PMRA 1223670, 1223682, 1223683 and 1231627). Study results revealed that along with the liver, the testes and epididymides were targeted in males while the uterus was targeted in females. An increased incidence of hyperplasia, benign Leydig-cell tumours, granulomas of the testes and reduced numbers of spermatozoa in the lumens accompanied by the presence of an increased number of early, nucleated sperm precursor cells in the epididymides were noted. In females, uterine adenocarcinomas were increased above the concurrent and historical control values. The effect of tralkoxydim on the metabolism of lipids, such as cholesterol, a precursor of androgens, estrogen and progestrogen, could play a key

role in the increased incidence of testicular and uterine alterations. No information is available to determine what role, if any, tralkoxydim may play in lipid metabolism. As well, no hormone measurements were available for tralkoxydim that might have helped to explain the interaction of tralkoxydim on the endocrine system.

The written comments received (PMRA 1790651) stated that the Leydig cell tumours are benign spontaneously occurring tumours in male rats. They commented that although these tumours are also observed in humans, they have a much higher incidence in rats than humans. Comments claimed the increased incidence was observed only at the high dose level of 2500 ppm which was considered excessive. They further support their position stating that tralkoxydim was not mutagenic and the related compounds clethodim and sethoxydim are not mutagenic or oncogenic.

In humans, approximately 1% of testicular tumours are Leydig cell adenomas (0.01% of all cancers in men). While human Leydig cell tumours are exclusively benign in children, approximately 10 to 15% can be malignant in adults (Kaplan et al., 1986; Grem et al., 1986). The diagnosis of Leydig cell tumours in laboratory animals is from histological evaluation while in humans it is common from palpation, after presentation of gynecomastia or an abnormal endocrine profile. For these reasons, small, benign Leydig cell adenomas that are not palpable may escape detection in humans (Clegg et al., 1997). While the reported human incidence is significantly less than the incidence seen in rodents, the true incidence of Leydig cell tumours may be higher in humans than previously thought and as a result can not be discounted.

The PMRA also did not agree with the statement that the high-dose level showed excessive toxicity in animals. In males, the number of mortalities was significantly lower than that seen in the control group and the effects on body weight were limited to decreased body weight gain which was not substantially different from the control group. As such, the benign Leydig cell tumours at the high-dose level were considered treatment related.

The PMRA is in agreement that with respect to tralkoxydim being non-mutagenic and the related compounds clethodim and sethoxydim also being non-mutagenic and showing no evidence of carcinogenicity.

Given that the comments did not include any mechanistic data to support a threshold approach, the PMRA will continue to use a linear low dose extrapolation approach for the cancer risk assessment of tralkoxydim.

6. Comment Relating to the Two Year Hamster Study, PRVD Sections: Health Considerations; 3.1; 3.2.2; Appendix IIIA

It was recommended that a margin of exposure approach instead of a linear risk assessment (Q*) approach for the 80 week carcinogenicity study conducted with hamsters be utilized for the cancer risk assessment of tralkoxydim since the uterine tumours are not considered to be treatment related.

PMRA Response

In the proposed re-evaluation decision document for tralkoxydim, a cancer risk assessment was conducted by the PMRA. It was stated that in the absence of mode of action data to support a threshold approach, a linear low dose extrapolation approach (Q*) would be used for the re-evaluation of tralkoxydim.

The PMRA concluded that the 80 week carcinogenicity study in Syrian hamsters was acceptable for risk assessment purposes (PMRA 1227525, 1227526, 1227527 and 1227528). In this study, the organs that were targeted by tralkoxydim in males included the liver, kidney and the testes as demonstrated by alterations in organ weights and histopathology (liver only). In tralkoxydim-exposed females, an increase in the weights of the liver, the uterus and the ovaries along with alterations in histopathology were noted. There were no treatment-related increases in the number of tumours in males. Females experienced an increase in the number of animals with hepatocellular adenomas (high-dose level) and benign uterine adenomas (high-dose level) as compared to controls. An increased number of benign sex cord stromal tumours of the ovary were also noted in mid- and high-dose females as compared to control animals. Based on the presence of a variety of tumours in female hamsters, tralkoxydim was considered to be tumourigenic in female hamsters.

The PMRA revisited the uterine tumour incidence and found that when the adenomas and adenocarcinomas were appropriately combined, there was a lack of treatment-related response. Thus, the PMRA accepts the argument that the occurrence of uterine tumours was not considered treatment related. However, no information was provided to dismiss the occurrence of liver and ovarian tumours in hamsters; therefore, these remain of concern.

Based on the previously mentioned points, the PMRA will continue to use a linear low dose extrapolation approach for the cancer risk assessment of tralkoxydim in hamsters.

7. Comment Relating to Food Residue Chemistry Summary, section 1.1.2, Appendix VI

An error was identified in the tralkoxydim PRVD, Appendix VI (Food Residue Chemistry Summary), section 1.1.2 relating to animal metabolism.

The PRVD indicated the following:

> "Given the results of the metabolism data, residues of tralkoxydim and its metabolites are expected to occur in very low amounts in livestock and the residue definition and MRL for animal commodities is required".

A residue definition and MRL for tralkoxydim in animal commodities is not required and therefore this statement should be revised to:

> "Given the results of the metabolism data, residues of tralkoxydim and its metabolites are expected to occur in very low amounts in livestock and the residue definition and MRL for animal commodities is **not** required".

References

Data submitted during consultation:

PMRA#1790659 Davies, D. 2000a. Tralkoxydim 400 g/l SC Formulation: In Vitro Absorption of Tralkoxydim Through Rat Epidermis. Zeneca Agrochemicals. CTL/JV1604/REG/REPT. Mar.21, 2000. Unpublished. PMRA#1790658

PMRA#1790657 Davies, D. 2000b. Tralkoxydim 400 g/l SC Formulation: In Vitro Absorption of Tralkoxydim Through Human Epidermis. Zeneca Agrochemicals. CTL/JV1603/REG/REPTt. Mar.21, 2000. Unpublished.

PMRA#1581315 Johnson, I. 2005. Tralkoxydim (Grasp 40SC): In Vitro Absorption of Tralkoxydim Through Human Epidermis. Syngenta Central Toxicology Laboratory. JV1883/Regulatory/Report. Dec.21, 2005. Unpublished.

PMRA#1131522 Prout, M.S. 1990. Tralkoxydim: In vivo Percutaneous Absorption Study in the Rat. ICI Central Toxicology Laboratory. Alderley Park MacClesfield, Cheshire, UK. Ctl ref: Y02140/057/001. CTL Study No: URO291. Unpublished.

Additional Information Considered – Published

Bronaugh R L, and Franz TJ (1986). Vehicle effects on percutaneous absorption. In vivo and in vitro comparisons with human skin. Br. J. Dermatol. 115: 1–11.

Clegg ED, JC Cook, RE Chapin, PMD Foster and GP Daston. 1997. Leydig cell hyperplasia and adenoma formation: mechanisms and relevance to humans. *Reproductive Toxicology*, 11: 107-121.

Kaplan GW, WJ Cromie, PP Kelalis, I Silber and ES Tank. 1986. Gonadal stromal tumours: A report of the prepubertal testicular tumour registry.

Grem JL, HI Ronins, KS Wilson, K Gilchrist and DL Trump. 1986. Metastatic Leydig cell tumour of the testis. Report of three cases and review of the literature. *Cancer Research*, 58: 2116-2119.

Additional Information Considered – Unpublished

NAFTA. 2008. Draft NAFTA Dermal Absorption Group Position Paper On Use of In Vitro Dermal Absorption Data in Risk Assessment. Unpublished.